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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,908	08/07/2003	Reinier Lh Bolhuis	2923-552	7844

6449 7590 06/20/2006

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,908	BOLHUIS ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-10 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-10 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 are under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite for reciting "a nucleotide sequence encoding the CDR3 region (designated H3), or/and encoding the CDR2 region (designated H2), or/and encoding the CDR1 region (designated H1), as shown in FIG. 1 or/and FIG. 6", because it is not clear as to what the CDRs regions are in figure 6. It is noted that figure 6 consists of a light chain and a heavy chain amino acid sequences, but does not clearly indicate the CDR regions.

Further, claim 1 is indefinite for reciting "at least one copy of a nucleic acid encoding the antigen-binding site of the light chain of an antibody comprising a nucleotide sequence encoding the CDR3 region (designated L3), or/and encoding the CDR2 region (designated L2), or/and encoding the CDR1 region (designated L1), as shown in FIG. 1 or/and FIG. 6", because figure 1 consists of the amino acid sequence only for the heavy chain variable region only, but not a light chain variable region. As written, the claims are not clear as to what the specific CDRs are for the light and heavy

chain variable regions. Appropriate correction is required, in addition the applicant is suggested to properly indicate the amino acid portions corresponding to the CDR regions and incorporate the SEQ ID NOs for the CDRs of the heavy and light chain variable regions.

Claim 6 is unclear for reciting "substantially does not alter", because it is not clear as to what the phrase "substantially does not alter the amino acid sequence" means. What does "substantially does not alter" mean? Does the applicant mean that the amino acid sequence has the same structure or function? It is not clear as to what physical or chemical properties are "not altered". Further, it is not clear as to what the word "alter" means. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant vector system comprising a nucleic acid encoding the antigen-binding site, wherein the antigen is G250, of the heavy chain of an antibody consisting of a nucleotide sequence encoding the CDR3 region (designated H3), and encoding the CDR2 region (designated H2), and encoding the

CDR1 region (designated H1), as shown in SEQ ID NO:6, and a nucleic acid encoding the antigen-binding site, wherein the antigen is G250, of the light chain of an antibody consisting of a nucleotide sequence encoding the CDR3 region (designated L3), and encoding the CDR2 region (designated L2), and encoding the CDR1 region (designated L1), as shown in SEQ ID NO:15, wherein the nucleic acid encoding the antigen-binding site of the heavy chain and of the light chain have separate expression control sequences, does not reasonably provide enablement for a recombinant vector system comprising at least one copy of a nucleic acid encoding the antigen-binding site of the heavy chain of an antibody comprising a nucleotide sequence encoding the CDR3 region (designated H3), or encoding the CDR2 region (designated H2), or encoding the CDR1 region (designated H1), as shown in FIG. 1 or/and FIG. 6, and at least one copy of a nucleic acid encoding the antigen-binding site of the light chain of an antibody comprising a nucleotide sequence encoding the CDR3 region (designated L3), or encoding the CDR2 region (designated L2), or encoding the CDR1 region (designated L1), as shown in FIG. 1 or/and FIG. 6, which does not contain a full set of six CDRs or any recombinant system that consists of a nucleic acid sequence encoding one CDR from light chain and one CDR from the heavy chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a recombinant vector system comprising at least one copy of a nucleic acid encoding the antigen-binding site of the heavy chain of an antibody comprising a nucleotide sequence encoding the CDR3 region (designated H3), or/and encoding the CDR2 region (designated H2), or/and encoding the CDR1 region (designated H1), as shown in FIG. 1 or/and FIG. 6, and at least one copy of a nucleic acid encoding the antigen-binding site of the light chain of an antibody comprising a nucleotide sequence encoding the CDR3 region (designated L3), or/and encoding the CDR2 region (designated L2), or/and encoding the CDR1 region (designated L1), as shown in FIG. 1 or/and FIG. 6, wherein the nucleic acid encoding the antigen-binding site of the heavy chain and of the light chain have separate expression control sequences.

The specification teaches a recombinant expression system consisting of a nucleic acid encoding the antigen binding site of the heavy chain of the antibody consisting of SEQ ID NO: 6 and a nucleic acid encoding the antigen binding site of the light chain of the antibody consisting of SEQ ID NO: 15. The specification fails to enable a recombinant vector system as claimed, wherein the nucleic acid encoding the antigen-binding site does not contain all six CDRs from SEQ I D NO:6 and SEQ ID NO:15.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. The specification provides no direction or guidance regarding how to produce all antibodies as broadly defined by the claims. Undue experimentation

would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

One of skill in the art would neither expect not predict the appropriate functioning of the antibody as broadly as is claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Weijtens et al (The Journal of Immunology, 157:836-843, 1996) as evidenced by the specification.

Claims 1-3 are drawn to a recombinant vector for the production of an antibody comprising the SEQ ID NO:15 as light chain variable region and SEQ ID NO:6 as heavy chain variable region. It is noted that the antibody comprising the SEQ ID NO:15 as light chain variable region and SEQ ID NO:6 as heavy chain variable region is the G250 monoclonal antibody (please see page 1 of the instant specification). Claims 4 and 5 are interpreted as drawn to a method for the recombinant production of the G250 monoclonal antibody by introducing the recombinant vector system into a host suitable host cell, wherein the host cell is a mammalian cell. Thus, the claims are interpreted as

drawn to a vector producing the G250 monoclonal antibody and a method of production of such antibody by introducing the recombinant vector system into a mammalian cell.

Weijtens et al teach lymphocytes that express a single-chain Fv receptor; wherein the genes encoding the VH and VL of the G250 monoclonal antibody were isolated from cDNA prepared from the G250 hybridoma producing cells and fused to the Fc(ε)RI signaling receptor y-chain of mast cells, introduced into a vector and expressed in lymphocytes (see entire document, particularly page 837 and page 836, right column). Thus, the lymphocytes expressing the scFv are eukaryotic cells derived from hybridoma cell DSM ACC 2526 obtained by transfer of the genetic material encoding the antigen-binding site (i.e., VH and VL) of the G250 antibody into the lymphocytes (i.e., receptor cell or cell derived from hybridoma DSM ACC 2526) which produce a single-chain antibody (i.e., scFv).

The product of the claims 1-3 is defined in terms of a laboratory designation rather than by physical characteristics, structure or even the process by which the product is prepared. Consequently, comparison of this product with the prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons. Thus a lesser burden of proof is required to make out a case of anticipation for a product claimed in terms of a laboratory designation than when claimed in conventional fashion by its physical characteristics, structure or even in terms of the process by which it is made.

Therefore, it is the Examiner's position that Weijtens et al have produced hybridomas which secrete antibodies that are directed to the same antigen that the

claimed antibodies bind. One of ordinary skill in the art would reasonably conclude that Weijtens et al's antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Weijtens et al have produced hybridomas that secrete antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed hybridoma and antibody with the hybridoma and antibody of Weijtens et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed hybridoma and antibody and the hybridoma and antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

As evidenced by the specification, the antibody comprising the SEQ ID NO:15 as light chain variable region and SEQ ID NO:6 as heavy chain variable region, which comprise the CDRs as claimed in the instant claims, is the G250 monoclonal antibody (please see page 1 of the instant specification) and since Weitjens et al teach the expression of G250 monoclonal antibody in mammalian cells (please see materials and methods), it is inherent that the antibody taught by Wietjens et al would have the same CDRs as of SEQ ID NO:6 and SEQ ID NO:15. Further, since Weitjens et al teach the expression of G250 antibody wherein the genes encoding the VH and VL of the G250 monoclonal antibody were isolated from cDNA prepared from the G250 hybridoma producing cells, introduced into a vector and expressed in lymphocytes, Weitjens et al read on the instant claims.

Therefore, Weitjens et al anticipate the claims.

7. Claim 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Carceller et al (U.S. Patent 5969107, Date Issued: October 19th, 1999).

Claims 1-5 have been described supra.

Carcellar et al teach an anti-idiotypic antibody comprising a CDR (H1 as shown in figure 1 of the instant application), and a vector system to produce such antibodies (please see paragraphs 9-13, in particular).

Due to the indefinite nature of the claims (please see above), wherein the claims recites "the heavy chain of an antibody comprising the nucleotide sequence ..... as shown in figure 1 or figure 6, and the light chain of an antibody comprising the nucleotide sequence ..... as shown in figure 1 or figure 6" and because figure 1 does not consist of a light chain and because figure 6 does not specifically assign the specific amino acid sequence for the CDRs; and furthermore since the claim does not specifically recite the particular antigen that the antibody binds to, the claim is interpreted as any antibody consisting of any of the CDRs selected from figure 1 or figure 6.

Thus the antibody of Carceller et al anticipates the claims because Carcellar et al teach an anti-idiotypic antibody comprising a CDR (H1 as shown in figure 1 of the instant application).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al (a) (WO 88/08854, Published 11/17/1988) as evidenced by the specification in view of Oosterwijk et al (b) (Seminars in Oncology. 1995. 22(1): 34-41) in view of Robinson et al (U.S. Patent 5,618,920; Issued 4/8/1997) and in view of Queen et al (U.S. Patent 5,530,101; Issued 6/25/1996).

Claims 1-5 and 10 are interpreted as being drawn to the nucleic acid sequence of the monoclonal antibody G250 and antibody fragments and the method of production of such antibody or antibody fragments. In addition, claims 6-9 are interpreted as a method wherein the antibody is humanized, wherein the antibody can be used as a diagnostic or therapeutic agent, coupled with a diagnostic marker, cytotoxic agent.

Oosterwijk et al (a) teach the hybridoma which produces monoclonal antibody G250 (please see entire document). Oosterwijk et al (a) further suggests the use of

G250 monoclonal antibody as a carrier agent of an anti-tumor drug therapy in renal cell carcinoma patients Oosterwijk et al (a) does not teach the nucleic acid sequence of the monoclonal antibody G250 and that the monoclonal antibody G250 can be used as a therapeutic agent or that the antibody can be humanized further couple it with a diagnostic marker or a cytotoxic agent.

Oosterwijk et al (b) teach the Use of Monoclonal Antibody G250 in the Therapy of Renal-Cell Carcinoma.

Robinson et al (see columns 12-22) teach Fv derived from a known antibody. Robinson et al teach Fv, determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce FV (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Ward et al teach vectors for producing FV.

Queen et al teach human antibodies and humanized antibodies comprising CDRs from non-human donor VH and VL chains, human framework and constant regions and the humanized antibody binds the same antigen an the non-human donor antibody, providing the CDRs (see column 2-3 and 12-16, in particular). Queen et al teach humanized antibodies and antigen-binding fragments thereof (i.e. single-chain antibodies) that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy as well as vectors and host cells for

expressing and producing the humanized antibodies including E.coli, yeast cells, myeloma cells and CHO-cells (see entire document, particularly column 2, columns 11, lines 18-34 and columns 16-18 and Examples).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to obtain the nucleic acids encoding the VH and VL from the G250 hybridoma taught by Oosterwijk et al (a) to produce the claimed nucleic acid sequence, and further humanize it as taught by Queen et al.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success at the time the invention was made to have obtained the nucleic acids of VH and VL from the G250 hybridoma, and utilize it for therapeutic purposes in view of Osoterwijk et al (a) as evidenced by the specification and Robinson et al, Queen et al and Osoterwijk et al (b) because Oostewijk et al teach the hybridoma which produces monoclonal antibody G250 and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as concensus sequences and specific oligonucleotide seuquences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Queen et al teach vectors and host cells including E.coli, yeast cells, myeloma cells and CHO-cells for expressing and producing humanized antibodies that are less immunogenic in human patients compares to mouse antibodies and hence,

better suited for human therapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known G250 monoclonal antibody and produce cells (i.e. host cells) including E.coli, yeast cells, myeloma cells and CHO-cells nucleic acids encoding humanized G250 antibodies and antigen-binding fragments thereof for therapy in renal cell carcinoma patients as taught by Osoterwijk et al (b) because humanized antibodies are less immunogenic in human patients compared to mouse antibodies and better suited for human therapy according to Queen et al. In addition, one of ordinary skill in the art would have been motivated at the time the invention was made to male the above modifications because Oosterwijk et al (a) suggests the use of G250 monoclonal antibody as a carrier agent of an anti-tumor drug therapy in renal cell carcinoma patients and Oosterwijk et al (b) teach the Use of Monoclonal Antibody G250 in the Therapy of Renal-Cell Carcinoma. Further Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity". Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known G250 antibody could be established from the G250 hybridoma using techniques disclosed in the references used in the instant rejection. Thus, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and VL from the G250 hybridoma,

wherein the monoclonal antibody G250 can be used in the therapy of Renal-Cell Carcinoma patients in view of Osoterwijk et al (a) as evidenced by the specification and Robinson et al, Queen et al and Osoterwijk et al (b).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Gorter et al. 1992. Clinical Experimental Immunology, 87:111-116.

2. Oosterwijk et al. 1986. Int. J. Cancer, 38:489-494.

3. Steffens et al. 1997. J. Clin. Oncol., 15:1529-1537.

4. Oosterwijk, E., et al. 1993. J. Of Clin. Oncol., 11:738-750.

Conclusion

11. No claims are allowed

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER